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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/668,196
Filing Date: September 22, 2000
Appellant(s): RUSSELL ET AL.

J. Patrick Finn III, PH.D.
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed September 3, 2004.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The brief does not contain a statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief. Therefore, it is presumed that there are none. The Board, however, may exercise its discretion to require an explicit statement as to the existence of any related appeals and interferences.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is substantially correct. The changes are as follows: With reference to Issue Number 3, it is noted that in the Final Action of November 2003, the rejection was not maintained over claims 18 and 19. See, Action of November 17, 2003, page 13. Thus, Issue 3 should refer to the subject matter of claims 1-7, 9, 11-17, 20-22, 24, 26, and 28-33, and should not include claims 18 and 19,

(7) Grouping of Claims

Appellant's brief includes a statement that claims 2-4, 6, 7, 11-22, 26, and 31-33 do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Bateman et al., "Fusogenic membrane glycoproteins as a novel class of genes for the local and immune-mediated control of tumor growth," Cancer Research, vol. 60 (March 15, 2000), pages 1492-97.

Wiebel et al., "Combined live measles-mumps virus vaccine," Archives of Disease in Childhood. vol. 48 no. 7 (July 1973), pages 532-36.

Linardakis et al., "Regulated Expression of Fusogenic Membrane Glycoproteins," Gene Therapy, vol. 6 supp. 1 (October 1999), page S4, abstract 13.

Bateman et al., "Fusogenic Membrane Glycoproteins- A Novel Class of cytotoxic Genes with immunostimulatory Properties," Gene Therapy, vol. 6 supp. 1 (October 1999), page S6, abstract 24.

Taqi et al., "Regression of Hodgkin's disease after measles," The Lancet, (May 16, 1981), page 1112.

Bluming et al., "Regression of Burkitt's lymphoma in association with measles infection," The Lancet, (July 10, 1971), pages 105-06.

Johnston et al., "A recombinant measles vaccine virus expressing wild-type glycoproteins: consequences for viral spread and cell tropism," Journal of Virology, vol. 73 no. 8 (August 1999), pages 6903-15.

Usonis et al., "Reactogenicity and immunogenicity of a new live attenuated combined measles, mumps and rubella vaccine in healthy children," Pediatric Infectious Disease Journal, vol. 18 no. 1 (January 1999), pages 42-48.

Asada et al., "Treatment of Human cancer with Mumps Virus," Cancer, vol. 34 no. 6 (December 1974), pages 1907-28.

Sato et al., "Attenuated Mumps virus therapy of carcinoma of the maxillary sinus," International Journal of Oral Surgery, vol. 8 no. 3 (June 8, 1979), pages 205-11.

Duprex et al., "Observation of measles virus cell-to-cell spread in astrocytoma cells by using a green fluorescent protein-expressing recombinant virus," Journal of Virology, vol. 73 no. 11 (November 1999), pages 9568-75.

Galanis et al., "Use of viral fusogenic membrane glycoproteins as novel therapeutic transgenes in gliomas," Gene Therapy, vol. 6 supp. 1 (October 1999), page S7, abstract 28.

Russell et al., Proceedings of the American Association for Cancer Research, vol. 41 (March 2000), page 259, abstract 1648.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

1) The rejection of claims 31 and 32 under 35 U.S.C. 112, first paragraph for lacking enablement.

Claim 31 and 32 read on methods of reducing the number of viable cancer cells in a mammal comprising the administration of an attenuated measles virus, wherein (claim 31) the virus comprises at least one point mutation, or (claim 32) the virus does not comprise contiguous point mutations. These claims are rejected for lack of enablement under 35 U.S.C. 112, first paragraph because the Appellant has not provided sufficient information to enable those in the art to make or use viruses as required by the limitations of these claims without undue experimentation.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

In the present case, the claims read on the use of any attenuated measles virus, which may comprise any of the types of mutations identified in claims 31 and 32. The application teaches the use of attenuated measles virus to reduce the number of viable cancer cells in a subject, and

teaches methods for screening for attenuated virus. However, the application does not teach any specific mutations, point mutations or otherwise, that may be used in the viruses to be used in the claimed methods.

While the claims do not require that the claimed mutations have any particular effect, such virus would be required to be attenuated in order to be useful in the claimed methods. However, the art teaches that certain mutations in the genome, even in comparison to the attenuated vaccine strains, could lead to viruses with increased pathogenicity. For example, Patterson et al. (J Virol 267(1): 80-9) teaches that certain recombinant viruses, derived from the Edmonston measles vaccine strain, have increased morbidity when administered in vivo in comparison to the parent vaccine strain. The reference therefore demonstrates that the effect of any additional mutations to even an attenuated strain may result in virus that are no longer attenuated, and may thus no longer qualify for use in the claimed methods. The art therefore demonstrates that there is at least some level of unpredictability in the art surrounding the claimed invention.

In addition to this, because of the breadth of the claims, the claimed mutations to the viral genome would also include mutations to the viral proteins. It is known in the art of protein mutation generally that the effects of such mutations tend to be unpredictable. See e.g., Bowie et al. Science 247(4948): 1306-10 (teaching that while proteins tend to be tolerant to substitutions, the effect of the substitution on the protein varies with the mutated residues ties role in the protein structure and function- and that, at present, it is not generally possible to predict such roles from sequence alone). Thus, the art teaches both that the effect of particular mutations to viral proteins is unpredictable, and that there is a similar unpredictability in the effect of point

mutations on a virus' ability to be used in the claimed methods. However, while the art is unpredictable, the Appellant has not provided any examples of specific point mutations that may be made, or provided any examples or guidance to noncontiguous mutations that may be made, to the measles virus genome so that the virus may be used in the claimed methods. In view of the unpredictability in the art, and the lack of any examples or guidance in the application as to what point mutations or contiguous mutations may be made to the attenuated virus, the Appellant has not provided sufficient information to enable those in the art to make or use any measles virus with any mutations such as those required in claims 31 and 32 without undue experimentation.

2) The rejection of claims 1-7, 9, 11-17, 20-22, 24, and 28-33 as being obvious under 35 U.S.C. 103(a).

Claims 1-7, 9, 11-17, 20-22, 24, and 28-33 are drawn to methods for the reduction of the number of viable cancer cells in a mammal through administration to the mammal of attenuated measles virus. These claims stand rejected as obvious over Bateman et al (Cancer Research 60:1492-1497- Bateman et al.) in view of Wiebel et al. (Arch. Dis. Childhood 48:532-536 1973). This rejection is made in further light of the supportive teachings of Linardakis (Gene Therapy 6(suppl):S4, abstract 13), the Bateman abstract (Gene Therapy 6(suppl):S6, abstract 24), Taqi (The Lancet, May 16, 1981, page 1112), Bluming (The Lancet, July 10, 1971, pages 105-106), and Johnston et al. (Journal of Virology 73(8): 6903-15).

Bateman et al. teaches administration of the viral fusogenic membrane glycoproteins as a therapeutic for control of tumor growth in a patient (see, abstract). The reference teaches that the

measles virus proteins kill target cells by inducing fusion, and that this activity can be exploited therapeutically to kill tumor cells. Page 1492 (the last two sentences of the first full paragraph); page 1493, Fig. 1; and pages 1495-1496. Bateman et al. teaches an exemplary cancer for therapeutic reduction as melanoma (see page 1492, last full paragraph). The reference differs from the claimed invention by teaching administration of the glycoproteins via transduction with plasmid DNA, rather than by administration of an attenuated strain of measles.

Weibel et al. teach commercially available preparations of attenuated measles virus either as a monovalent preparation of the Moraten line of measles virus (ATTENUVAX) or as a trivalent preparation of measles, mumps, and rubella (MMR) (see page 532, the abstract and first two paragraphs, and page 533, the second paragraph). Weibel et al. teach administration of the Virus Preparations as Vaccines.

From these teachings, it would have been obvious to those in the art to substitute the attenuated virus of Weibel for the plasmid DNA of Bateman et al. This is because, from the Bateman article, it would have been clear to those in the art that what is important to the treatment is the insertion of the measles virus DNA into the tumor cells to be killed. The plasmids used in the reference were just a convenient vector. This was highlighted by the teachings of both Linardakis and the Bateman abstract, which suggest the use of viral vectors to introduce the DNA into cells. Thus, it would be obvious to one of ordinary skill in the art to use the attenuated measles virus taught by Weibel as a convenient vector for the measles virus DNA.

One of ordinary skill in the art would have had a reasonable expectation of success due to the suggestions in the art of the use of viral vectors for the introduction of the measles virus DNA. Further, the art also has examples of live measles virus as effective in causing the

regression of cancers. See Taqi and Bluming. From these additional references, one of ordinary skill in the art would have had further grounds for believing that the use of an attenuated measles virus as a vector would have no effect on the operability of the measles virus DNA to destroy cancer cells. As both the whole virus and the isolated DNA have been shown to reduce tumors, there would be no reason for one of ordinary skill in the art to expect anything but success in the use of an attenuated virus as a vector for the DNA.

3. The rejection of claims 1-7, 9, 11-17, 20-22, 24, 26 and 28-33 as being obvious under 35 U.S.C. 103(a).

Claims 1-7, 9, 11-17, 20-22, 24, and 28-33 have been described above. Claim 26 further limits the claimed methods to embodiments wherein the vaccine comprising the attenuated measles virus is the MMR-II vaccine. These claims were rejected over the teachings of Bateman et al. in view of Usonis (Ped Inf Dis J 18: 42-48), and in light of Linardakis, the Bateman abstract, Taqi, Bluming, and Johnston. The teachings of the references other than Usonis have been described above. These other references suggest the use of attenuated measles virus as an effective vector for the delivery of fusogenic measles proteins to kill cancer cells.

Usonis teaches two vaccine compositions combining measles, mumps, and rubella live attenuated viruses, the MMR 11 vaccine comprising the Enders Edmonston measles strain and the PRJORIX vaccine comprising the Schwartz measles strain. See, page 42, the abstract and first paragraph of the introduction, and page 43, column 2, second from last paragraph). The reference teaches that these compositions may be safely administered to humans with few adverse symptoms. It would have been prima facie obvious to one of ordinary skill in the art to

have used one of the vaccine compositions taught by Usonis as a safe, convenient, and effective means of administering the measles fusogenic glycoproteins for control of cancer growth in a patient.

4. The rejection of claims 16 and 17 as being obvious under 35 U.S.C. 103(a).

Claims 16 and 17 further limit the claimed methods to embodiments wherein the measles virus is provided in a composition also comprising both attenuated mumps and rubella virus, or comprising attenuated rubella virus, respectively. These claims were rejected over the teachings of Bateman et al. in view of either Usonis or Weibel, further in view of either Asada (Cancer 34:1907-28) or Sato (Int J Oral Surg 8:205-11), and in light of Linardakis, the Bateman abstract, Taqi, Bluming, and Johnston. The teachings of the references other than Asada and Sato have been described above. The teachings of the previously cited references indicate that administration of attenuated measles virus would be an effective method of reducing the number of cancer cells in a mammal. Additionally, Weibel and Usonis indicate that attenuated measles viruses are often found in formulations of combined attenuated Measles, Mumps, and Rubella vaccines.

In addition to these teachings, each of the Sato and Asada references indicate that the Mumps virus also has anticancer activities. From these references, those in the art would be motivated to use a combination of attenuated Measles and Mumps virus. As such a composition is easily available in the form of the known measles, mumps, and rubella vaccines, those in the art would be motivated to use such compositions as a convenient composition for treatment of cancers using the attenuated measles and mumps viruses.

5. The rejection of claims 18 and 19 as being obvious under 35 U.S.C. 103(a).

Claims 18 and 19 further limit the claimed methods to embodiments wherein the attenuated measles virus is modified so as to express a marker polypeptide, and in particular to express one of the marker polypeptides β-galatosidase or Green Fluorescent Protein. These clams stand rejected over the teachings of Bateman et al. in view of either Usonis or Weibel, further in view of Duprex (J Virol 73:9568-75), and in light of Linardakis, the Bateman abstract, Taqi, Bluming, and Johnston. The teachings of the references other than Duprex have been described above. These references suggest the use of attenuated measles virus for the reduction of the number of cancer cells in a mammal, but do not alone suggest the modification of the virus to express a marker polypeptide.

Duprex teaches that measles virus can be recombinantly made to express the marker polypeptide, green fluorescent protein, and that expression of green fluorescent protein can be used to monitor cellular infection of the measles virus in vivo. See, page 9568, abstract, and page 9574, last paragraph. In view of these teachings, it would have been obvious to those in the art to include such a marker polypeptide in an attenuated measles virus so that the infection and destruction of cancer cells by the virus (i.e. the efficacy and progression of treatment) could be monitored. Those in the art would have had a reasonable expectation of success in such a combination due to the teachings of Duprex indicating the GFP would allow such in vivo monitoring. The teachings of Duprex in combination with the references cited above would therefore have rendered the methods of claims 18 and 19 obvious to one of ordinary skill in the art.

6. The rejection of claim 20 as being obvious under 35 U.S.C. 103(a).

Claim 20 further limits the claimed methods to embodiments wherein the attenuated measles virus is used to reduce the number of cancer cells, including embodiments wherein the cancer cells are glioma cells. These clams stand rejected over the teachings of Galanis et al. (Gene Therapy 6 (Supp 1): S7, abstract 28) or Russell et al. (Proc. Am Assoc Cancer Res 41: 259, abstract 1648) in view of either Wiebel or Usonis, and further in light of the teachings of Linardakis, the Bateman abstract, Taqi, Bluming, and Johnston. The teachings of the references other than the Galanis and Russell references have been described above. As described above, these later references teach the use of attenuated measles virus to reduce the number of cancer cells in a mammal because the attenuated virus would be an obvious vector for the expression of the measles virus fusogenic proteins in the cancer cells. Each of Galanis and Russell indicate that these fusogenic proteins are effective to kill glioma cells. It would therefore have been obvious to those in the art that glioma cells are a type of cancer that maybe treated by the methods suggested by the other references.

Those in the art would have had a reasonable expectation of success for the same reasons as indicated above, and because the Russell and Galanis references indicate that the fusogenic proteins are effective to kill glioma cells. Thus, the teachings of these references in view of those cited above would have rendered obvious the use of attenuated measles virus to reduce the number of glioma cells.

(11) Response to Argument

1) The rejection of claims 31 and 32 should be maintained over Appellant's argument in traversal.

As indicated above, claims 31 and 32 were rejected as lacking enablement because the claims are broadly drawn to methods of using any measles virus with the types of mutations identified in the claims. However, in addition to the fact that the application neither provides any examples of such mutations that may be used, nor provides any guidance as to what mutations may be made such that the resulting virus may be used in the claimed methods, the art teaches that there is a high level of unpredictability in the making of mutations to virus. The art indicates both that the mutation of viral proteins (encoded by the mutated genome) may have unpredictable results, and that the mutation of even an attenuated viral genome absent teachings as to which mutations to make may result in virus with increased pathogenicity.

The Appellant traverses this argument of the basis that "A person having ordinary skill in the art at the time the Appellant's filed would have been able to obtain an attenuated measles virus containing point mutations." While the Examiner agrees that those in the art would be able to obtain attenuated measles virus without undue experimentation, such virus may or may not contain point mutations or non-sequential point mutations as required by the claims. It is known in the art how to passage virus in order to achieve attenuated virus. However, such a mode of operation is not dependant on the type of mutation made to the viral genome. In order to make and use attenuated virus according to claims 31 and 32, those in the art would be required to first make a virus with specific point mutation, of which there are many thousand possible variations within the genome, and determine which of these is attenuated. There is no guidance in the

application as to which of the many possible mutations would result in an attenuated virus. Further, as was described in the prior action, the effect of any particular point mutation on the viral activity is unpredictable. In view of the broad scope of the claims, the unpredictability of the affect of any particular point mutation, and the lack of guidance in the application, there is little evidence that those in the art would be able, without undue experimentation, to make attenuated virus with the specific types of mutations required by claims 31 and 32. Because the Appellant has provided no evidence to the contrary, the rejection is maintained.

2) The rejection of Claims 1-7, 9, 11-22, 24, 26, and 28-33 as obvious under 35 U.S.C. 103(a) should be maintained over the prior art of record.

These claims are drawn to methods for the reduction of the number of viable cancer cells in a mammal through administration to the mammal of attenuated measles virus. They stand rejected as obvious over Bateman et al in view of Wiebel. This rejection is made in further light of the supportive teachings of Linardakis, the Bateman abstract, Taqi, Bluming, and Johnston. In the Appeal Brief, the Appellant has presented three arguments in traversal of the rejection. These arguments may be summarized as follows: A) the teachings of the prior art follow a different protocol from the claimed method, B) there is no suggestion in the cited references for the use of an attenuated measles virus to reduce the number of viable cells in a mammal, and C) the Appellant's invention is non-obvious over the prior art for both demonstrating a surprising result, and satisfying a long felt need in the art. The arguments are not found persuasive.

The protocol used by the Appellant does not adequately distinguish from the prior art.

The Appellant's first argument in traversal of the rejection states "the claimed invention is very different from the prior art." They argue that "killing cells in a dish and treating animals with a transfected tumor cells are vastly different from administering an attenuated measles virus to a mammal to reduce the number of viable cancer cells." However, while the Bateman et al. reference does not teach the administration of attenuated measles virus to a mammal, the teachings of the reference are directed to the use of proteins encoded by viral genes (including the measles virus) to kill tumor cells. See, abstract, and page 1495. The reference also suggests the delivery of the DNA encoding the proteins to the tumor cells in vivo. Page 1497. Thus, while the reference uses different protocols to test the efficacy of the DNAs in treating tumors, these protocols are merely experimental, and not intended to mimic modes of in vivo treatment directly. Rather, by suggesting the delivery of the DNAs to the tumor cells in vivo, the reference is teaching a method with similarity to the claimed methods. While the reference does not teach the administration of attenuated measles virus to tumor cells, the reference does suggest the administration of genes of the measles virus to the cells. Thus, the Appellant's argument that different protocols are used in the reference and the claims is not found persuasive as the reference is suggesting a similar protocol to the claimed methods.

The Appellant also seems to be arguing that a correction to a subtitle and an experimental protocol within the reference is evidence that the reference should not be applied against the claimed invention. However, the correction does not alter any of the suggestions made in the Abstract or the Discussion of the reference. The purpose of the correction is solely to correct the experimental protocols used by the authors in support of their conclusions. It in no way alters the

conclusions that the FMG encoding genes may be used to kill tumor cells in vivo through direct administration of the genes to the cells.

Finally, while it is recognized that the reference does not, alone, suggest the administration of attenuated measles virus to treat tumors, this is not deemed persuasive in overcoming an obviousness rejection based on a combination of references. The Appellant's first argument in traversal should therefore not be found persuasive.

The cited references suggest to one or ordinary skill in the art the use of attenuated measles virus to kill tumor cells.

The Appellant next argues the references cited in the actions fail to teach or suggest the use of attenuated measles virus to treat mammalian tumors. The Appellant is correct in that none of the references explicitly indicates that those in the art may reduce the number of tumors in a mammal through the administration of attenuated measles viruses. However, the motivation to combine the knowledge of the prior art need not be explicit in the references cited in support of the rejection. See, MPEP § 2144 (citing numerous decisions by the Federal Circuit and the USPTO Board of Patent Appeals and Interferences in support of this position). Such motivation may also be found, for example, in logic and sound scientific principle. In re Soli, 137 USPQ 797, at 801 (CCPA 1963). Thus, while the Office acknowledges that no one of the cited references states that one in the art may administer an attenuated measles virus to a mammal to reduce the number of cancer cells in the animal, this is not deemed dispositive of whether the art as a whole suggests the claimed invention.

As indicated in the prior actions, and by the Appellant's summary of the reference, Bateman et al. suggests the administration of genes encoding viral fusogenic proteins (FMGs), including those from the measles virus, to cancer cells such that the cells are killed. Weibel teaches that attenuated measles virus may be safely administered to humans. From these two references alone, there may be inadequate motivation to administer the attenuated viruses to humans to kill cancer cells. However, these references are not being considered in a vacuum.

As indicated above, one of ordinary skill in the art would be aware of the teachings of Bateman et al. indicating that the administration of viral (including Measles virus) FMGs is effective to kill tumor cells, and the teachings of Weibel regarding the safety of the attenuated Measles virus. Those in the art would also be aware of the teachings of the Bluming and Taqi references, which indicate that infection by the Measles virus has the side effect of also inducing regression of cancers.

With reference to these two references, the Appellant argues that those in the art reading these references would not be adequately motivated to administer attenuated virus to treat reduce the number of viable cancer cells. Brief, page 9. However, at the time the Appellant filed, those in the art would be faced not only with the separate teachings of Taqi and Bluming, but with these observations in view of the later teachings regarding Measles virus FMGs. Those in the art are at this point faced with teachings that a specific set of Measles virus gene products are useful to kill cancer cells, and teachings that the whole live virus apparently has the same result. It is also clear from the references that new methods of delivering the genes to cells were desired. See, Linardakis and the Bateman abstract, each suggesting the use of viral vectors to deliver the

genes. From these teachings, it would be obvious to those in the art that the use of the attenuated Measles Viruses would be likely candidates for use in such cancer treatments.

The use of the attenuated virus as convenient vectors for the administration of FMGs to cancer cells is suggested by the additional teachings in the art that wild-type Measles virus infections also induces cancer regression, and that the FMG proteins (the F and H proteins) are necessary for the viral infection of cells. See e.g. Johnston, page 6903 (teaching both the F and H proteins are required for viral cell induced fusion, and that attenuation likely results from modification of proteins controlling other functions that envelope fusion with the target cell). As attenuated virus particles require active fusogenic proteins to be infectious, such particles would be obvious and convenient vectors for the delivery of the FMG genes to cells. Thus, while no one of the references explicitly suggests the use of attenuated Measles virus to treat cancers, or as vectors for the Measles FMG genes, the use of these attenuated particles would have been obvious from the combined teachings of the art.

Those in the art would have had a reasonable expectation of success in the use of the attenuated virus because they would recognize that attenuated viruses that carry the fusogenic proteins required both for the anti-cancer activity and virus infectivity, could be used to deliver the proteins and genes to the target cells. This expectation is further supported by the evidence that live Measles viruses have been shown to have the desired anti-cancer activity. Thus, those in the art would have expected that attenuated virus would cause cancer regression in a manner similar to either the isolated FMG DNAs, or the wild-type Measles virus. The Appellant's argument that the identified references do not suggest the claimed inventions should therefore not be found persuasive.

There is insufficient evidence of secondary indicia of non-obviousness to support withdrawal of the rejection.

The Appellant's final argument in traversal is that, even if the references do suggest the claimed invention, the invention is still non-obvious as having achieved unexpected results, and as fulfilling a long felt need in the art. In this argument, the Appellant asserts that two secondary considerations provide further evidence of the nonobviousness of the claimed methods. The Appellant argues first that they achieved an unexpected result in demonstrating that attenuated measles virus resulted in the regression of cancers. The Appellant also argues that the claimed methods satisfy a long felt need in the art by reciting a method for the reduction of viable cancer cells. These arguments are not found persuasive because the Appellant has neither established that it was unexpected that an attenuated Measles virus would have anti-cancer activities, nor established a nexus between the long-felt need for cancer treatments and the presently claimed methods of treating cancers.

With respect to the unexpected results argument, the Appellant has not demonstrated that it was in fact unexpected that the administration of an attenuated Measles virus would result in the regression of cancers. As indicated in the references cited above, it was known in the art both that Measles virus infections had, in several instances, resulted in the regression of cancers. It was also more recently discovered that a particular set of Measles genes and proteins (the FMG genes and proteins) were apparently the source of this anticancer activity. Given that those in the art were aware of these facts, and as it was recognized that the attenuated viruses had active F and H proteins (Johnston, crossover paragraph of pages 6903-04), the fact that the attenuated

virus would have the same anti-cancer activities as the MG compositions and the wild-type virus would not have been unexpected.

The long-felt need argument is likewise flawed. Evidence of long-felt need requires more than an assertion that the Appellant has provided a solution to a general problem in the art. In the present case, while there has been a general and long-felt need for cancer treatments, there has not been a long-felt need for the specific treatment claimed by the Appellant. In addition to the development of several treatments for cancers in the art other than the methods currently claimed, there is also no history of failures by those in the art attempting to use viruses to treat cancer. Rather, there has been a progression in the art both in the treatment of cancers generally, and in the use of attenuated viruses to treat cancers, and more recently of the use of viral FMGs and experiments with modes of delivery. See e.g., Reichard et al, J Surg Res 52:448-53 (of record in the IDS filed on Jan 5, 2001). Thus, the Appellant has not demonstrated that there was a long-felt need in the art for viral based cancer therapies. Further, as demonstrated by the Bateman references, the use of Measles virus DNA and proteins to treat cancers was already known in the art. Further, the use of FMGs to treat cancers was relatively new in the art. This tends to indicate that the need met by the present invention, that of delivering the FMG compositions to cancer cells, was not a long-felt need, but one that had only recently arisen. The Appellant has therefore not established that there was a long-felt and unsolved need in the art prior to, and solved by, the Appellant's invention.

Dependent Claims

In the Brief, the Appellant argues that the inventions of claims 6, 7, 11, 12, 13, 14, 15, 16, 17, 18 and 19, 20, 21, 22, 31, 32, and 33 stand or fall separately. The Appellant argues that the combination of references cited above does not render the additional teachings of these claims obvious.

It is noted that, while the Appellant also argues that claims 2-4 stand or fall separately from the other claims, there is no discussion of the merits of the rejection with respect to these claims. Rather, the Appellant merely asserts that the art does not teach the methods limitations of these claims. These claims describe the claimed methods wherein the virus is administered directly to cancer or tumor cells, or into a tumor. However, in view of the teachings in the art that the purpose of the administration of the virus is to infect the cancer cells so as to deliver the FMG encoding DNA into the cells, it would have been obvious to those in the art to deliver the virus as close as possible to the cells so as to increase the efficacy of the treatment by insuring as many of the virus as possible actually infect the target cells. Thus, the claimed methods of administering the virus to the cells or the tumor would have been obvious to those in the art.

Claims 6 and 7 further limit the claimed methods by methods of administration of the virus to the mammals being treated. The Appellant argues that the references do not teach these modes of administration of the virus. However, such modes would have obvious to those in the art. The methods of claim 6 of continuously administering the virus to the mammal, and of claim 7, wherein the viruses are administered in pulses, are methods of administration known in the art. It would have been obvious to those in the art to continuously administer the virus until such time as the treatment has been effective. The administration by pulsing (and devices to do so) is acknowledged by the Appellant on page 16-17 as known in the prior art. It is submitted that use

of such methods would be obvious to those in the art as routine methods of administration, and as modes of optimization of the treatments.

Claims 11-15, and 33 further limit the claimed methods to embodiments with ranges of effective dosages of the attenuated virus. The Examiner would like to point out that the Appellant has pointed out on page 16 of the specification that is known in the art that the safe doses of Measles virus range from between 10^3 to 10^{12} pfu, and that the dosages of the measles virus administration to treat cancer cells varies from patient to patient. The Examiner is therefore not persuaded by the Appellant's traversal and maintains the rejection of these claims as obvious optimization of the method of treatment.

Claims 16 and 17 read on the claimed methods wherein the attenuated measles viruses are administered in combination with attenuated mumps and rubella viruses, or in combination with attenuated rubella viruses. The Appellant argues that the identified references do not teach the administration of such viruses to treat cancers. Because the references suggest the use of attenuated Measles virus, and teach compositions comprising these viruses that also comprise the other identified viruses, it would have been obvious to those in the art to administer such vaccines to treat cancer as a convenient Measles containing composition.

Claims 18 and 19 read on embodiments wherein the attenuated virus is modified to express a marker polypeptide. The Appellant argues that the cited references do not teach or suggest such a limitation. The Examiner agrees. The rejection as to these two claims is therefore withdrawn.

Claims 20, 21, and 22 further limit the methods to the treatment of general types of cancers. The Appellant argues that the references do not teach the administration of attenuated

Measles viruses to treat any of these forms of cancers. However, as the references suggest, as indicated above and in the prior actions, the administration of attenuated Measles virus to treat tumors generally. See e.g., Bateman et al., abstract, teaching the FMGs are useful for the control of tumor growth, without limitation; and the teachings of Taqi and Bluming indicating that the Measles virus proteins would be effective against different types of cancers. The Appellant's traversal is therefore not found persuasive, and the rejection is maintained against these claims.

Claims 31 and 32 further limit the claimed method to embodiments wherein the attenuated measles virus comprises at least one point mutation, or wherein the virus comprises at least point mutation, but no contiguous point mutations. The Appellant argues that the art does not suggest the use of such attenuated measles viruses to treat cancer. However, the art, in suggesting the use of attenuated measles viruses to treat cancer as indicated above, indicates that any attenuated Measles virus may be used, so long and the FMG genes and proteins are operative. It is known in the art that attenuated virus may result from point mutations in the viral genome. See e.g., Collins et al., WO 97/22032, pages 33-34 (Of record in the July 2002 IDS- demonstrating that the temperature sensitive attenuated phenotype of RSV is due to a single point mutation. In vies of this knowledge in the art, and the teachings indicating that attenuated measles virus may be used to reduce the number of cancer cells, it would have been apparent to those in the art that attenuated virus comprising such mutations could be used. In view of this, it would have been obvious to those in the art to use any such attenuated Measles virus, including those with point mutations, and those without contiguous point mutations.

3) The rejection of Claims 1-7, 9, 11-17, 20-22, 24, 26 and 28-33 as obvious under 35 U.S.C. 103(a) should be maintained over the prior art of record.

The claims have been described above. These claims were rejected over the teachings of Bateman et al. in view of Usonis, and in light of Linardakis, the Bateman abstract, Taqi, Bluming, and Johnston. The Appellant traverses the rejection of these claims on the same grounds as argued with respect the rejection of claims 1-7, 9, 11-22, 24, 26, and 28-33 above. These arguments should not be found persuasive with regards to the instant rejection for the same reasons as indicated with respect to the rejection above.

4) The rejection of Claims 16 and 17 as obvious under 35 U.S.C. 103(a) should be maintained over the prior art of record.

These claims are drawn, respectively, to the claimed methods wherein the attenuated measles virus are provided in a composition with either attenuated mumps and rubella virus, or attenuated rubella virus. They stand rejected over the teachings of Bateman et al. in view of either Usonis or Weibel, further in view of either Asada or Sato. The teachings of these references are also considered in light of Linardakis, the Bateman abstract, Taqi, Bluming, and Johnston. The Appellant traverses the rejection of these claims on the same grounds as argued with respect the rejection of claims 1-7, 9, 11-22, 24, 26, and 28-33 above, and by arguing that these references do not teach or suggest the use of a composition comprising attenuated measles virus in combination with attenuated mumps virus, or attenuated rubella virus for the reduction of the number of viable cancer cells in a mammal. In particular, the Appellant argues that the Asada and Sato references "fail to correct the deficiencies" of the previously cited references.

This argument should not be found persuasive with regards to the instant rejection for the same reasons as described above.

5) The rejection of Claims 18 and 19 as obvious under 35 U.S.C. 103(a) should be maintained over the prior art of record.

Claims 18 and 19 describe the methods above wherein the attenuated measles virus is modified so as to express a marker polypeptide, and in particular to express one of the marker polypeptides β-galatosidase or Green Fluorescent Protein. They stand rejected over the teachings of Bateman et al. in view of either Usonis or Weibel, and further in view of Duprex. The teachings of these references are also read in light of the teachings of Linardakis, the Bateman abstract, Taqi, Bluming, and Johnston. The Appellant appears to traverse the rejection of these claims on the same grounds as argued with respect the rejection of claims 1-7, 9, 11-22, 24, 26, and 28-33 above. This argument should not be found persuasive with regards to the instant rejection for the same reasons as described above.

6) The rejection of Claim 20 as obvious under 35 U.S.C. 103(a) should be maintained over the prior art of record.

Claim 20 reads on the method described above, wherein the attenuated measles virus is used to reduce the number of cancer cells, including embodiments wherein the cancer cells are glioma cells. The claim stands rejected over the teachings of Galanis or Russell, in view of either Wiebel or Usonis. The teachings of these references are also read in light of the teachings of Linardakis, the Bateman abstract, Taqi, Bluming, and Johnston. The Appellant traverses this

rejection on substantially the same grounds as argues with respect to the rejection over Bateman et al. in view of Usonis or Weibel, and in light of the teachings of Linardakis, the Bateman abstract, Taqi, Bluming, and Johnston as described above. This argument should therefore not be found persuasive with regards to the instant rejection for the same reasons as described above.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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